

European Patent Office

Office européen des brevets

(ii) Publication number:

021 121

BI

1

# **EUROPEAN PATENT SPECIFICATION**

(B) Date of publication of patent specification: 11.06.83

(b) tmt. Q2.7: C 07 D 253/06. A 61 K 31/53

(f) Application number: 80103032.1

22) Date of filling: 30.05.80

- 1.2.4-Triszine derivatives, process for preparing such compounds and pharmaceutical compositions containing them.
- @ Priority: 01.06.79 GB 7919257
- (8) Date of publication of application: 07.01.81 Bulletin 81/1
- 49 Publication of the grant of the patent: 11.05.83 Bulliotin 83/19
- Designated Contracting States: BE CH DE FR GB LI LU NL SE
- References cited:
  AT B 190 941
  CH A 511 216
  DE A 1 802 364
  GB A 769 014
  GB A 1 223 481
  GB A 1 318 845
  US A 2 952 677

- (3) Proprietor: THE WELLCOME FOUNDATION LIMITED
  183-193 Eusten Road
  London NW1 28P (GB)
- (7) Inventor: Baxter, Martin George 34 Whitehead Close Wilmington, Dartford, Kent (GB) Inventor: Elphtok, Albert Reginald 51 Baring Hood Lee, Lendon, S.E. 12 (GB) Inventor: Miller, Allatair Alasile 91 Elmahurst Gardens Tombridge, Kent (GB) Inventor: Sewyer, David Alan 60 Bourne Vale Hayes, Kent (GB)
- (2) Representative: Berg. Wilhelm, Dr. et al., Dr. Berg, Dipi.-Ing. Stapf, Dipi.-Ing. Schwabe, Dr. Dr. Sandmair Maueridrcherstrasse 45 D-8000 München 80 (DE)

Note: Within nine months from the publication of the mention of the grant of the European petent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 89(1) European patent convention).

Courier Press, Learnington Spa, England

EP 0 021 121 B1

#### 021 121

1,2,4-Triszine derivatives, process for preparing such compounds and pharmaceutical compositions containing them

The present invention relates to a group of novel compounds which are useful in the treatment of CNS disorders, such as epilepsy, to phermaceutical compositions containing them, and to methods for their preparation.

U.K. Patent No. 769,014 discloses compounds of the formula (I):

10

88

$$H_2N \longrightarrow N \longrightarrow X$$

wherein X and Y are hydrogen and/or halogen atoms, as having activity against bacterial and malarisi Infections in animals. This patent specifically discloses those compounds wherein X and Y are both 18 hydrogen stoms, wherein X is a hydrogen atom and Y is a 4-chloro atom, and wherein X is a 4-chloro

etom and Y is a 2-chloro and 3-chloro atom, respectively.

Rece et al. J. Mad. Chem. 1972 16, 869, have shown that these compounds, and in particular the 4-chlorophenyl and the 3/A-dichlorophenyl compounds are active against the malaris organism Plesmodium berghel in mice. However, these two compounds were also shown to be toxic at curative does and presumably were not investigated further because of their low therapeutic ratio in this context. The 2.A-dichlorophenyl compound had only slight entimalarial activity. The therapeutic ratio of the compounds were such as to prevent their use in human medicine for the treatment or prophylexie of melaria and they were not progressed further.

US Patent No. 3,637,688 discloses compounds of the formula (II):

$$H_2N = N + R^3$$

$$R^4 = R^3$$
(fi)

wherein R1 is hydrogen or fluorine, and R2, R4 and R4 are hydrogen, fluorine or trifluoromethyl provided that at least one of  $R^1$ ,  $R^3$ ,  $R^3$  and  $R^4$  is fluorine or trifluoromathy), as being useful in the treatment of malaria. In the Ress article referred to above, the 4-trifluoromathylphenyl compound (i);  $H^2 = CF_p$ ,  $R^1 = R^2 = R^4 = H$ ) was alaimed to be less toxic than the chlorophanyl compounds whilst still being active against malaris. The other fluoro and triffuoromathyl compounds referred to in the article

were substantially less active than the 4-trifluoromethylphenyl compound.

Resemburg and Bottiroli *Proc. Soc. esp. Biol.*, 1984, *115*, 410, described a series of tests in which three enti-melarial agents, quinacrine, chloroquine and hydroxychloroquine, were tested as anti-

convulsants. Only hydroxychloroquine possessed a favourable activity profile. It has now been discovered that a group of novel 3,5-diamino-6-(substituted phemyl)-1,2,4trizzines are active in the treatment of CNS disorders, such as psychiatric and neurological disorders, and are particularly useful as anticonvulsants, for example in the treatment of epilepsy. Furthermore, these triazines are believed to be nondepressant at likely therapeutic dose levels and therefore are advantageous as compared with depressant antiepliaptics such as phenobarbitons

Accordingly the present invention provides a compound of the formula (III):

$$H_2N \xrightarrow{N} H_2 = N \xrightarrow{R^3} R^5$$

or an acid addition salt thereof, wherein R<sup>o</sup> is chlorine, bromine, lodine, C<sub>1-4</sub> alkyl or trifluoromethyl; R<sup>7</sup> is hydrogen, halogen C<sub>1-4</sub> alkyl or trifluoromethyl or R<sup>0</sup> and R<sup>7</sup> form a —CH—CH—CH—CH— group optionally substituted by a halogen stom or a C, alkyl or trifluoromethyl group,

 $R^0$  is hydrogen, bromine, lodine,  $C_{1-4}$  alkyl or trifluoromethyl,  $R^0$  is hydrogen, halogen,  $C_{1-4}$  alkyl or trifluoromethyl,  $R^{10}$  is hydrogen, methyl, or fluorine and  $R^{11}$  is an emino,  $C_{1-4}$  acylamino or di-substituted' aminomethyleneamino group provided that, at most, only two of  $R^2$ — $R^{10}$  are other than hydrogen and that  $R^7$ — $R^{10}$  are not all hydrogen when  $R^0$  is chlorine.

Suitably the C<sub>1-2</sub> alkyl group is a methyl group.

Suitably R<sup>2</sup> is a chlorine or brombie atom or a methyl or trifluoromethyl group or is linked to R<sup>7</sup> to form a -CH-CH-CH-group and preferably R<sup>a</sup> is a chlorine or bromine atom or linked to R<sup>7</sup> to form a -CH-CH-CH-group.

Preferably R7 and R8 are each hydrogen, chloring or bromine atoms.

Preferably R<sup>6</sup> is a hydrogen or bromine atom.

Suitable substituents for the aminomethylene amino group are  $C_{s-4}$  alkyl groups or a  $-(CH_s)_s - CH_s$  group wherein X is 0, S, NH or CH<sub>s</sub> group and n is the integer 1 or 2. Suitably  $R^{11}$  is an amino, acetamido or dimethylaminomethyleneamino group and preferably  $R^{11}$  is an amino group.

When three of the substituents Re....R<sup>10</sup> are other than hydrogen, it is preferred that R<sup>3</sup> and R<sup>10</sup> are hydrogen and that Ra, RI and Ra are those halogen atoms previously defined and in particular chlorine

Preferred compounds of the formula (III) Include: 3,5-diamino-6-(2,3-dichloropherryi)-1,2,4-triazine 3,5-diamino-6-(2,5-dichloropherryi)-1,2,4-triazine 3.5-dlamino-6-(4-bromo-2-chlorophanyl)-1,2,4-triazine 3,5-dlamino-8-(5-bromo-2-chlorophanyi)-1.2,4-triazine 3,5-dlamino-8-(2,3,5-trichlorophenyi)-1.2,4-triazine 3,5-diamino-8-(2-chioro-8-fluorophenyi)-1,2,4-triazine 3,5-diamino-8-(2-methylphenyl)-1,2,4-triazine
3,5-diamino-8-(2-trifluoromethylphenyl)-1,2,4-triazine
3,5-diamino-8-(2-tromophenyl)-1,2,4-triazine
3,5-diamino-8-(2-tromophenyl)-1,2,4-triazine
3,5-diamino-8-(2-tripluoromethyl)-1,2,4-triazine

3,5-diamino-8-(2-bromo-5-chlorophanyl)-1,2,4-triazine
3,5-diamino-8-(1-haphthyl)-1,2,4-triazine
8-ecetamido-3-amino-8-(2,3-dichlorophanyl)-1,2,4-triazine

3-emino-8-(2,3-dichlorophenyl)-6-dimethyleminomethyleneamino-1,2,4-triazine
3,5-diamino-8-(2-methyl-1-naphthyl)-1,2,4-triazine
3,5-diamino-8-(3-chloro-1-naphthyl)-1,2,4-triazine.

The present invention also provides the first practicable medical use of the compounds of the formula (iii), as hereinbefore defined. Preferably this will be for the treatment of CNS disorders, and in particular apliapsy, in humana.

in a further espect, the present invention provides pharmaceutical formulations comprising a compound of the formula (III) in admixture with a pharmaceutically acceptable carrier. Suitable acid addition saits of the compounds of formula (III) include those formed with both organic and inorganic ecids. Such acid addition salts will normally be pharmacoutically acceptable. Thus, preferred salts include those formed from hydrochloric, sulphuric, citric, tertaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumeric, maleic, oxaloacetic, methanesulphonic, p-tolusnesulphonic and benzenesulphonic acids.

The compounds of the formula (iii) will be present in the compositions of the present invention in an effective unit dosage form, that is to say in an amount sufficient to be effective against CNS disorders in

The pharmsceutically acceptable carriers present in the compositions of this invention are materials recommended for the purpose of administering the medicament. These may be liquid or solid materials, which are otherwise inert or medically acceptable and are compatible with the active

These pharmaceutical compositions may be given orally or parenterally, used as a suppository, or applied topically as an ciriment, cream or powder. However, and and paranteral administration of the

compositions are preferred.

For oral administration, fine powders or granules will contain diluting, dispensing and/or surface active agents, and may be presented in a draught, in water or in a syrup, in capsules or sachets in the dry state or in non-equipous suspension wherein suspending agents may be included, or in a suspension in water or syrup. Where desirable or necessary, flavouring, preserving, suspending, thickening or emulalfying agents can be included.

When a suspension is prepared in water according to the present invention at least one such

agents will be present.

For parenteral administration, the compounds may be presented in sterile aqueous injection solutions which may contain anti-oxidents or buffers.

As stated above, the free base or a salt thereof may be administered in its pure form unassociated with other additives in which case a capsule or sachet is the preferred carrier.

Alternatively the active compound may be presented in a pure form as an effective unit desage. for instance, compressed as a table t or the like.

Other compounds which may be included are, for example, medically inert ingredients, e.g. solid and liquid diluents such as lactose, starch, or calcium phosphate for tablet or capsules; clive gli or ethyl oleate for soft capsules; and water or vegetable oil for suspensions or emulsions; fubricating agents such as talc or magnesium stearete; gelling agents such as colloidal clays; thickening agents such as gum tregacanth or sodium alginate; and other therapeutically acceptable accessary ingredients such as humactants, preservatives, buffers, and antioxidants which are useful as carriers in such formulations.

Tablets or other forms of presentation provided in discrets units may conveniently contain an amount of compound of the formula (III) which is effective at such desage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 250 mg.

The pharmaceutical compositions of the present invention will be prepared by the admixture of a compound of the formula (III) with a pharmaceutically acceptable carrier. Conventional pharmaceutical exciplents may be admixed as required.

The present invention provides a method of treatment of convulsions in mammals, and particularly epilepsy in humans by the administration of a non-toxic enticonvulsant effective amount of a compound of the formula (iii) or a pharmaceutically acceptable sait, or a composition as hereinbefore defined.

As indicated above, the compounds of the formula (III) are generally useful in treating such ze disorders by oral administration or injection (i.p. or s.c.).

The compounds of the formula (iii) are normally administered orally at a dose of from 0.1 mg/kg. to 30 mg/kg. per day. The dose range for south humans is generally from 8 mg. to 2,400 mg/day and preferably 35 to 1,050 mg/day. Due to the fact that the compounds of the formula (iii) are extremely long softing, it may often be advantageous to administer an initial dose of 70 to 2,400 mg. the first day then a lower dose of 20 to 1,200 mg. on subsequent days.

The present invention also provides a process for the preparation of compounds of the formula (III) which comprises the cyclisation of a compound of the formula (IV):

wherein R<sup>4</sup>—R<sup>10</sup> are as itereinbefore defined; and thereafter, where desired substituting the amino group adjacent to the phenyl ring to give a group R<sup>11</sup> wherein R<sup>11</sup> is as hereinbefore defined other than amino, by conventional methods.

This cyclisation reaction is normally carried out by refluxing in an alkanol, preferably a C<sub>1-4</sub> sikanol such as mathenol or athanol, in the presence of a strong base such as potassium hydroxide.

The preparation of the compounds of the formula (IV) is analogous to that described in the literature, i.e. U.S. Patent No. 3,837,688, for structurally related compounds.

The following examples illustrate the preparation of the compounds of the invention and their CNS sotivity.

### Example 1

Preparation of 3,5-diamino-8-(2,3-dichioruphenyl)-1,2,4-triazine. 2,3-Dichioruphenzoic Acid

A solution of 2.3-dichloroiodobenzens (37.3 g, 0.14M) in additum dried other (300 mls) was added dropwise to magnesium turnings (3.65 g, 0.15 gm Atm) and a crystal of iodine with warming so as to form a Grignard reagent.

The mixture was stirred and refluxed for 2 hours then cooled and transferred dropwise, under nitrogen; into a stirred mixture of sodium dried ether (250 mis) containing solid carbon dioxide (ca. 100 g). The mixture was stirred for 2 hours, left overnight to warm to room temperature, then treated with ice (ca. 150 g) and 2N equeous hydrochloric sold (75 mis), and the product extracted with ether (200, 100 and 50 mis). The combined ether extracts were washed with water (2 x 40 mis) then repeatedly extracted with 2N equeous sodium hydroxide (100, 50 and 50 mis). These basic solutions were combined, stirred with activated charcosl (3 g) for 10 minutes, filtered and the cooled filtrate was soldified with concentrated hydrochloric acid (25 mis) at 10°C. The resultant solid was filtered off, washed with water (2 x 20 mis) and dried in vacuo. Yield 20.78 g (77.6%), m.p. 167—169°C (uncorrected).

2,3-Dichlorobenzoyi Chloride

A mixture of 2.3-dichlorobenzolo sold (39.4 g 0.2M) and thionyl chloride (100 mis) was heated to reflux for 2‡ hours. The cooled solution was evaporated down in vacuo and distilled under nitrogen. Yield 35.5 g (85%), b.p. 148-148°C at 31 mm of mercury pressure.

2.3-Dichieroberzoyi Cyanida
A macure of cuprous cyanida (36.9 g, 0.41M), potassium todida (68.5 g, 0.41M) and xylena
A macure of cuprous cyanida (36.9 g, 0.41M), potassium todida (68.5 g, 0.41M) and xylena (400 mis) was refluxed in an atmosphere of nitrogen under a Dean and Stark trap for 24 hours so as to remove all trace of water.

A solution of 2,9-dichlorobenzoyl chioride (38.5 g, 0.17M) in sodium dried xylene (130 min) was added dropwise to the above mixture of dry cuprous cyanide and sylene. The resulting mixture was stirred and heated to reflux for a further 72 hours. The cooled mbiture was filtred and the solid washed well with sodium dried xylene (200 mb). The filtrate and washings were combined and evaporated down in vacuo to give an oil. Yield 32 g (94%).

3,5-Diamino-6-(2,3-dichiorophenyi)-1,2,4-triszina

3,0-Ummno-0-12,3-arenoropnanyu-1,2,4-arezuna
A solution of 2,3-dichioroberaroyi cyanide (32 g, 0.16M) in dimethylaulphoxide (80 mls) was added dropwise to a stirred suspansion of aminoguanidine blearbonate (81.67 g, 0.6M) which had been treated with 8N aqueous nitric acid (400 mls) at a temperature of ca 25°C. The mixture was stirred for 3 hours, then left to stand at room temperature for 7 days. The cooled mixture was stirred and basified with 0.880 aqueous ammonis (400 mls) at 20°C, then attred with ice cooling for 30 minutes, filtered and the resulting solid weshed thoroughly with water and finally dried in vacuo.

The above solid was added to a 10% solution of potassium hydracide pelists in methanol (400 mis) and the solution heated to refluxed for 1½ hours. When cool the solution was evaporated down in vacuo, treated with ice water (800 mis) then attired for 30 minutes and filtered. The residue was dried and recrystallised from teopropanol to give 3,6-diamino-6-(2,3-dichlorophenyi)-1,2,4-triazine. Ytald 6.8 g (15.6%), m.p. 216—218°C (uncorrected).

Example 2

By a method analogous to that described in Example 1 the compounds listed in Tables 1 and 2 were prepared:

TABLE 1

V; R	m.p. (uncorrected)	% Yield (from sold)
2,5-Ol <sub>2</sub> .	228-230°C 2	
2C1, 4Br	228-225°C	8
2-C1, 5-Br	288-240°C	2
2-CF,	177178°C	0,4
2-C1, 8-F	228228°C	14.5
2-Me	161189°C	25.
2-Br	204–207°C	. 34
2∤	219-222°C	7
2-Br, 5-Cl	255—256°C	1.2

TABLE 2

VI; A	m.p. (uncorrected)	% Yield (from sold)
н	215216°C	7.5
2-Mo	191194°C	0.3
3_CI	285-288°C	1.0

# Example 3

Preparation of 3,5-diamino-6-(2,3,5-trichiorophenyi)-1,2,4-triszine 2.3.5-Trichlorobenzoic Acid

Powered sedium nitrite (37.0 g, 0.54M) was added portionwise to concentrated sulphuric sold (270 ml) which was stirred under an atmosphere of nitrogen. The temperature of the mixture was not allowed to rise above 70°, Meanwhile 3-amino-2,5-dichlorobenzolo sold (100 g, 0.45M) was dissolved in hot gladel scatte sold (1,200 mil), the resultant solution was cooled rapidly to room temperature and added dropwise to the shove stirred and cooled nitrous sold mixture so that the internal temperature did not rise above 30°. The solution formed after the addition was left at room temperature for 2 hours then was slowly added to a stirred solution of cuprous chloride (97 g. 0.97M) in concentrated hydro-

chloric acid (970 ml). The resultant mixture was stirred until the nitrogen evolution had ceased and was then left overnight. The solid was filtered off, washed well with water and dried in vacuo. Yield 90.1 g (89%) m.p. 164—165°C (uncorrected).

2,3,6-Trichiorobenzoyi Chloride

10

18

20

A mbdure of 2,3,5-trichlorobenzoic scid (90 g. 0.4M) and dimethylformamide (1 mi) in thionyl chloride (200 mi) was heated to reflux for 2 hours. The cooled solution was evenorated down in vacuo and the residue distilled under nitrogen. Yield 89.2 g (90%), b.p. 158—160°C at the pressure of 30 mm of mercury.

2,3,5-Trichiorobenzoyi Cyanida

A mixture of cuprous cyanide (89 g. 0.9M), potassium iodide (150.5 g. 0.9M) and xylane (800 ml) was heated to reflex in an atmosphere of nitrogen under a Dean and Stark trap for 24 hours.

A solution of 2,3,5-trichlorobenzoyi chloride (89 g, 0.36M) in sodium dried xylene (100 ml) was added to the above suspension. The resulting mixture was attired and heated to reflux for a further 72 hours. The cooled mixture was filtered and the solid was washed well with addium dried sylans (200 mi). The filtrate and washings were combined and evaporated in vacuo to give an cit. Yield 78 g

3,5-Diamino-6-(2,3,5-trichlorophenyi)-1,2,4-triazine

A solution of 2,3,5-trichlorobenzoyi cyanida (38.5 g, 0.18M) in dimethytsulphoxida (80 ml) was added dropwise to a stirred suspension of aminoguanidine bicerbonate (65.76 g, 0.32M) which had been treated with 8N equeous nitric sold (580 ml). The mixture was attired for 3 hours and than was left to stend at room temperature for 21 days. The solid was filtered off, washed with water  $(2 \times 100 \, \mathrm{mi})$  and dried in vacuo. A suspension of the dried solid in a 10% solution of potessium hydroxide pellets in methenol (320 ml) was heated to reflux for 1 hour, the mixture was cooled and evaporated down in vacuo. The residue was treated with ice/water (200 ml), the resultant solid was filtered off and dried in vacuo. This dried solid was put on top of a dry column (25 mm diameter, 200 g of MFC silica gal) and eluted with a solution of stryl acetate/mathanol/acetic acid (80:2.5:2.5).
Fractions 50 to 80 (900 drops per fraction) were collected, combined and evaporated down in vacuo. The resultant solid was recrystallised from isopropanol to give 3,5-diamino-8-(2,3,5-trichiore-phenyi)-1,2,4-triazine. Yield. 0.77 g (1.6%), m.p. 232—235°C (uncorrected).

### 021 121

Example 4
Properation of 5-Acetamido-3-amino-8-(2,3-dichicrophenyi)-1,2,4-triazine

A solution of 3,6-diamino-8-(2,3-dichlorophenyt)-1,2,4-triazine (2 gm, 8mM) and acetic anhydride (10 mls) in acetic sold (20 mls) was attred and hested to reflux for 2 hours. The solution was then cooled and evaporated down in vacuo. The residue was treated with equeous 0.880 ammonia (100 mls) and the resultant mixture was attreed for 2 hours. The solid was separated by filtration, dried then recrystalized from isopropanol to give 6-acetamide-3-amine-6-(2,3-dichlorophenyl)-1,2,4-triazina. Yield 1.0 gms (42%), m.p. 250-252° (uncorrected).

Example 5 Preparation of 3-Amino-8-(2,3-dichlorophenyt)-5-dimethyl eminomethyleneamino-1,2,4-triazina cocelete

Dimethylformamide dimethyl sostal (1 ml) was added dropwise to a stirred mixture of 3,5-diamino-6-(2,3-dichlorophany0-1,2,4-triazine (1 g, 4miM) in dry dimethylformamide (20 mls) in a nitrogen strateghere. The mixture was stirred and heated at 120° for 2 hours, the the resultant solution was cooled and evaporated down in vecto. The residual oil was washed once with water (20 mis) than dissolved in a solution of oxelic acid (1 gm) in mathenol (20 mis). Ether (100 mis) precipitated an oil which slowly crystallized. The residue was recrystallized from equeous isoproperol to give 3-emino-6-(2,3-dichlorophenyl)-5-dimethylaminomethylenesmino-1,2,4-triazine oxelets. Yield 0.19 gme (14%), m.p. 172-175°C Dec. (uncorrected).

Ехатріе 6

Pharmacological Activity of Compounds of the Present Invention

Tables 3 and 4

The ambonyulsant activity of certain compounds of the present invention was determined by a standard maximal electroshock test, that described by L. A. Woodbury and V. D. Davenport, Arch. Int. Pharmacodyn.: 1952, 92, 97.

TABLE 3

۷۱Í; R¹	VIÎ; R	ED <sub>rs</sub> , MES mics, mg/kg, p.c.
2,3-Cl,	NH,	2.4
2,8GI,	NH <sub>a</sub>	3.3
2-Me	NH,	15.0
2-CI, 4-Br	NH,	12.8
2-CI, 6-Br	NH,	6.0
2-CF,	NH,	. 20.0
2-CI, 5-F	NH <sub>2</sub>	12.2
2,3,6Cl,	NH <sub>2</sub>	0.85
2Br	NH <sub>3</sub>	. 8.5
21	NH,	11.8
2-Br, 5-€I	NH,	4.8
2,3-Cl <sub>3</sub>	NHCOCH,	5
2,3-Cl,	N-CHNMe <sub>1</sub>	5

### 0 21 121

# TABLE 4

VIII R	ED <sub>los</sub> ME3 mice, mg/kg, p.o.
н	2.9
2-Me	· 16.5
3CI	. 0.5

The LD<sub>scr</sub> (expressed in mg/kg, p.o.) of 3,5-diamino-8-(2,3-dichlorophenyl)-1,2,4-trisxine and 3,5-diamino-6-(2,5-dichlorophenyl)-1,2,4-trisxine were determined in mice and rate. The LD<sub>sc</sub> described is the dose for which 50% of the animals survive 10 days after administration of the compound.

VII R <sup>s</sup>	R	Mice	Rate
2,3-Cl <sub>2</sub>	" NH,	250	640
2,5Cl <sub>2</sub>	NH <sub>a</sub>	708	· 640

3,5-Dismino-5-(2,3-dichlorophenyi)-1,2,4-triazina 150 mg

Lectore 200 mg

Maite Starch 50 mg

Polyvinyipyrrolidone 4 mg

Magnesium Stearate 4 mg

The drug was imbed with the lastose and starch and granulated with a solution of the polyvinylpyrrollidors in water. The resultant granulas were dried, mixed with magnesium stears and compressed to give tablets of average weight 408 mg.

#### 50 Claims

# 1. A compound of the formula (III):

bromine, boline,  $C_{1-4}$  alkyl or trifluoromethyl;  $R^a$  is hydrogen, halogen,  $C_{3-4}$  alkyl or trifluoromethyl;  $R^{ab}$  is hydrogen, methyl or fluorine and  $R^{11}$  is amino,  $C_{1-4}$  acylamino or di-substituted aminomethylene-amino, provided that at most only two of  $R^7$ — $R^{19}$  are other than hydrogen and that  $R^7$ — $R^{19}$  are not sill hydrogen when  $R^a$  is chlorine.

3. 3,5-Dismino-8-(2,3-dichiorophenyi)-1,2,4-triazine.

4. A phermaceutical composition comprising a compound of the formula (III), as claimed in any of claims 1 to 3 herein, in edmbture with a phermaceutically acceptable carrier.

E. A compound of the formula (iii), as claimed in any one of claims 1 to 3 herein, for use in

8. A compound of the formula (III) as claimed in any one of claims 1 to 3 for use in medicine in the rearmant of epilepsy.

18. A compound of the formula (III) as claimed in any one of claims 1 to 3 for use in medicine in the rearmant of epilepsy.

7. A process for the preparation of a compound of the formula (iii), as claimed in claim 1 herein, which comprises the cyclication of a compound of the formula (IV):

wherein  $R^a = R^{to}$  are as defined in claim 1 herein; and thereafter, where desired, substituting the amino group adjacent to the phenyl ring to give a group  $R^{t1}$  wherein  $R^{t1}$  is as defined in claim 1 herein other than amino, by conventional methods.

# **Patentansprüchs**

20

1. Verbindung der Formel (III)

$$H_{2N} \xrightarrow{N} H_{2N} \xrightarrow{R^{0}} H_{2N} \xrightarrow{R^{0}}$$

oder ein Säursadditionssalz deven, worin R<sup>e</sup> Chlor, Brom, Jod, C<sub>1-4</sub>-Alkył oder Triffuormethyl; R<sup>7</sup> Wasserstoff, Halogen, C<sub>1-4</sub>-Alkył oder Triffuormethyl oder R<sup>e</sup> und R<sup>7</sup> gemeinsem eine —CH—CH—CH—CH—Gruppe, die gegebenenfalls durch ein Halogenatom oder eine C<sub>1-4</sub>-Alkył oder Triffuormethylgruppe substituiert ist, R<sup>e</sup> Wasserstoff, Brom, Jod, C<sub>1-4</sub>-Alkył oder Triffuormethyl, R<sup>e</sup> Wasserstoff, Methyl oder Triffuormethyl, R<sup>e</sup> Wasserstoff, Methyl oder Fluor und R<sup>e</sup> Amino, C<sub>1-4</sub>-Asylamino oder disubstituiertes Aminomethylenamino, mit der Maßgabe bedeuten, daß höchstens zwei der Gruppen R<sup>e</sup> bis R<sup>es</sup> von Wasserstoff verschieden eind und daß nicht sämtliche Gruppen R<sup>e</sup> bis R<sup>es</sup> Wasserstoff bedeuten, wenn R<sup>e</sup> Chlor darstellt.

2. Verbindung der Formsi (ill) gemäß Anspruch 1, dadurch gekennzeichnet, daß R<sup>e</sup> ein Chior- oder Brometon dersteilt, R<sup>r</sup> ein Wesserstoff-, Chior- oder Brometon bedeutet oder R<sup>e</sup> mit R<sup>r</sup> unter Bildung einer —CH—CH—CH—CH—Gruppe verbunden sind, R<sup>e</sup> ein Wesserstoff-, Chior- oder Brometon darstellt, R<sup>e</sup> ein Wasserstoff- oder Brometon bedeutet und R<sup>11</sup> eine Aminogruppe derstellt.

3. 3,5-Diamino-6-(2,3-dichlorphenyl)-1,2,4-triazin.

4. Pharmazeutische Zubereitung entheitend eine Verbindung der Formel (iii) gemäß einem der Ansprüche 1 bis 3 zusammen mit einem pharmazeutisch annehmbaren Träger.

6. Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medi-

6, Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medizin bei der Behandlung der Epilepsie.

7. Verfahren zur Herstellung einer Verbindung dar Formel (III) gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel (IV)

in der R<sup>e</sup> bis R<sup>ro</sup> die in Anspruch 1 angegebenen Bedeutungen besitzen, cyclisiert und anschließend ge-würschtenfalls die dem Phanyiring benachbarts Aminogruppe in an sich bekannter Weise unter Bildung einer Gruppe R11, die die in Anspruch 1 angegebenen Bedeutungen besitzt, jedoch von einer Ammogruppe verschieden ist, substituiert.

# Revendications

25

## 1. Composé de formulo (III):

$$H_2N = N = N = R^5$$
 (III)

ou sel d'addition d'acide de celui-ci où Re représente un atome de chlore, de brome ou d'lode ou un radical alcoyle en C, ou trifluoromáthyle;

R<sup>7</sup> représente un atome d'hydrogène ou d'halogène ou un redical alcoyle en C<sub>1...a</sub> ou triffuorométhyle ou

blen Roet Romant un radical ---CH---CH---CH--- éventuellement substitué par un atome d'halogène

ou un radical alcoyle en C<sub>1-4</sub> ou trifluorométhyle, P<sup>e</sup> raprésente un atome d'hydrogène, de brome ou d'iode ou un radical alcoyle en C<sub>1-4</sub> ou trifluoro-

R<sup>o</sup> représente un atome d'hydrogène ou d'halogène ou un radicel alcoyle en C<sub>1-4</sub> ou trifluorométhyle, R<sup>o</sup> représente un atome d'hydrogène, un radical máthyle ou un atome de fluor, et

R<sup>11</sup> représents un radice! amino, C<sub>1-a</sub> acylamino ou aminométhylèneamino disubstitué, à la condition qu'eu maximum deux d'entre R<sup>2</sup>—R<sup>10</sup> représentent autre chose que des atomes d'hydrogène et que R<sup>2</sup>—R<sup>10</sup> ne représentent pas tous des atomes d'hydrogène lorsque R<sup>2</sup> représents un atome de chiore.

2. Composé de formule (III) suivant la revendication 1, cù R<sup>2</sup> représents un atome de chiore de chiore.

brams, R<sup>7</sup> représents un storns d'hydrogène, de chlors ou de broms ou blen R<sup>6</sup> est uni à R<sup>7</sup> pour formsr un radical -- CH--CH--CH--CH--, Re représente un etome d'hydrogène, de chlore ou de brome, Re représente un atome d'hydrogène ou de brome et R14 représente un radical amino.

3. La 3,5-diamino-6-(2,3-dichiorophényi)-1,2,4-triszine.

4. Composition pharmaceutique comprenant un composé de la formule (III), suivant l'une quelconque des revendications 1 à 3, à l'état de mélange avec un excipient pharmaceutiquement accept-

8. Composé de la formule (III), sulvant l'une qualconque des revendications 1 à 3, pour une application en médecina.

6. Composé de la formule (III), sulvant l'une quelconque des revendications 1 à 3, pour une application en médecine dans le traitement de l'épilepsis.

7. Procédé de préparation d'un composé de la formule (III), suivant la revendication 1, qui comprend la cyclisation d'un composé de formule (IV):

#### 021 121

où Re....R<sup>to</sup> sont tels que définis dans la revendication 1 et ensuite, al la chose est désirée, la substitution du radical amino adjecent su radical phényle pour la formation d'un radical R<sup>11</sup>, où R<sup>11</sup> est tel que défini dans la revendication ci-dessus et est autre qu'un radical amino, suivant des techniques classiques.

20

(ii) Publication number:

0 021 121

B1

0

# **EUROPEAN PATENT SPECIFICATION**

(i) Date of publication of patent specification: 11.05.83

(f) Int. Cl.2: C 07 D 253/06,

(1) Application number: 80103032.1

A 61 K 31/53

22 Date of filing: 30.05.80

- (8) 1.2.4-Triazine derivatives, process for preparing such compounds and pharmaceutical compositions containing them.
- (11) Priority: 01.06.79 GB 7919257
- (3) Date of publication of application: 07.01.81 Bulletin 81/1
- (9) Publication of the grant of the patent: 11.05.83 Bulletin 83/19
- Designated Contracting States: BE CH DE FR GB LI LU NL SE
- (B) References cited:

AT-8-190941

CH - A - 511 216

DE-A-1 802 384

GB-A-789 014

GB-A-1 223 491 GB-A-1 318 645

US-A-2952677

- (3) Proprietor: THE WELLCOME FOUNDATION LIMITED 183-193 Euston Road London NW1 2BP (GB)
- (1) Inventor: Baxter, Martin George 34 Whitehead Close Wilmington, Dartford, Kent (GB) Inventor: Elphick, Albert Reginald 51 Baring Road Lee, London, S.E. 12 (GB) Inventor: Miller, Alistair Ainslie 91 Elmshurst Gardens Tombridge, Kent (GB) Inventor: Sawyer, David Alan 60 Bourne Vele Hayes, Kent (GB)
- (1) Representative: Berg, Wilhelm, Dr. et al, Dr. Berg, Dipl.-Ing. Stapf, Dipl.-Ing. Schwabe, Dr. Dr. Sandmair Mauerkircherstrasse 45 D-8000 München 80 (DE)

Note: Within nine months from the publication of the mention of the grant of the European petent, any person may give notice to the European Petent Office of opposition to the European petent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

Courier Press, Learnington Spa, England

1,2,4-Triazine derivatives, process for preparing such compounds and pharmaceutical compositions containing them

The present invention relates to a group of novel compounds which are useful in the treatment of CNS disorders, such as epilepsy, to pharmaceutical compositions containing them, and to methods for their preparation.

U.K. Patent No. 759,014 discloses compounds of the formula (I):

10

$$H_2N \xrightarrow{N} \begin{array}{c} NH_2 \\ N-N \end{array}$$

wherein X and Y are hydrogen and/or halogen atoms, as having activity against bacterial and malerial infections in animals. This patent specifically discloses those compounds wherein X and Y are both hydrogen atoms, wherein X is a hydrogen atom and Y is a 4-chloro atom, and wherein X is a 4-chloro atom, and Y is a 2-chloro and 3-chloro atom respectively.

atom and Y is a 2-chloro and 3-chloro atom, respectively.

Rees et al, J. Med. Chem. 1972 15, 859, have shown that these compounds, and in particular the 4-chlorophenyl and the 3,4-dichlorophenyl compounds are active against the malaria organism Plasmodium berghei in mice. However, these two compounds were also shown to be toxic at curative doses and presumably were not investigated further because of their low therapeutic ratio in this context. The 2,4-dichlorophenyl compound had only slight antimalarial activity. The therapeutic ratio of the compounds were such as to prevent their use in human medicine for the treatment or prophylaxis of malaria and they were not progressed further.

US Patent No. 3,637,688 discloses compounds of the formula (II):

$$H_2N \xrightarrow{N} H_2 \xrightarrow{R^4} R^2$$

$$H_2N \xrightarrow{R^4} R^3$$
(III)

wherein  $R^1$  is hydrogen or fluorine, and  $R^2$ ,  $R^2$  and  $R^4$  are hydrogen, fluorine or trifluoromethyl provided that at least one of  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  is fluorine or trifluoromethyl, as being useful in the treatment of malaria. In the Rees article referred to above, the 4-trifluoromethylphenyl compound (II;  $R^2 = CF_3$ ,  $R^1 = R^3 = R^4 = H$ ) was claimed to be less toxic than the chlorophenyl compounds whilst still being active against malaria. The other fluoro and trifluoromethyl compounds referred to in the article

were substantially less active than the 4-trifluoromethylphenyl compound.

Rosenburg and Bottiroll *Proc. Soc. exp. Biol.*, 1964, 115, 410, described a series of tests in which three anti-malarial agents, quinacrine, chloroquine and hydroxychloroquine, were tested as anti-convulsants. Only hydroxychloroquine possessed a favourable activity profile.

It has now been discovered that a group of novel 3,5-diamino-8-(substituted phenyl)-1,2,4-triazines are active in the treatment of CNS disorders, such as psychiatric and neurological disorders, and are particularly useful as anticonvulsants, for example in the treatment of epilepsy. Furthermore, these triazines are believed to be nondepressant at likely therapeutic dose levels and therefore are advantageous as compared with depressant antiepileptics such as phenobarbitone.

Accordingly the present invention provides a compound of the formula (III):

$$H_2N = N = N = R^{11} R^{10} R^{8}$$
 $R^{8}$ 
 $R^{8}$ 
 $R^{8}$ 
 $R^{8}$ 
 $R^{8}$ 

or an acid addition sait thereof, wherein  $R^a$  is chlorine, bromine, indine,  $C_{1-4}$  alkyl or trifluoromethyl;  $R^a$  is hydrogen, halogen  $C_{1-4}$  alkyl or trifluoromethyl or  $R^a$  and  $R^a$  form a —CH=CH—CH=CH— group optionally substituted by a halogen atom or a  $C_{1-4}$  alkyl or trifluoromethyl group,

 $R^{s}$  is hydrogen, bromine, iodine,  $C_{1-a}$  alkyl or trifluoromethyl,  $R^{s}$  is hydrogen, halogen,  $C_{1-a}$  alkyl or trifluoromethyl,  $R^{10}$  is hydrogen, methyl, or fluorine and  $R^{11}$  is an amino,  $C_{1-a}$  acylamino or disubstituted aminomethyleneamino group provided that, at most, only two of  $R^{2}-R^{10}$ 

are other than hydrogen and that R'-R10 are not all hydrogen when R0 is chloring.

Suitably the  $C_{1-4}$  alkyl group is a methyl group. Suitably  $R^a$  is a chlorine or bromine atom or a methyl or trifluoromethyl group or is linked to  $R^7$  to form a —CH=CH—CH=CH— group and preferably R<sup>8</sup> is a chlorine or bromine atom or linked to R<sup>7</sup> to form a —CH=CH—CH=CH— group.

Preferably R7 and R6 are each hydrogen, chlorine or bromine atoms.

Preferably R<sup>8</sup> is a hydrogen or bromine atom.

Suitable substituents for the aminomethylene amino group are  $C_{1-4}$  alkyl groups or a  $-(CH_2)_2 \times (CH_2)_n$ — group wherein X is O, S, NH or CH<sub>2</sub> group and n is the integer 1 or 2. Suitably R<sup>11</sup> is an amino, acetamido or dimethylaminomethyleneamino group and preferably R<sup>11</sup> is an amino group.

When three of the substituents R9-R10 are other than hydrogen, it is preferred that R5 and R10 are hydrogen and that R6, R7 and R6 are those halogen atoms previously defined and in particular chlorine

Preferred compounds of the formula (III) include: 3,6-dlamino-6-(2,3-dichlorophenyi)-1,2,4-triazine

3,5-dlamino-6-(2,5-dichlorophenyi)-1,2,4-triazine

3,5-dlamino-6-(4-bromo-2-chlorophenyi)-1,2,4-triazine

3,5-diamino-6-(5-bromo-2-chlorophenyi)-1,2,4-triazine

3,5-diamino-6-(2,3,5-trichlorophenyi)-1,2,4-triazine

3,5-diamino-6-(2-chloro-6-fluorophenyl)-1,2,4-triszine

3,5-diamino-6-(2-methylphenyl)-1,2,4-triazine

3,5-diamino-6-(2-trifluoromethylphanyl)-1,2,4-triazine

3,5-diamino-6-(2-bromophenyi)-1,2,4-triazine

3,5-diamino-6-(2-iodophenyl)-1,2,4-triazine

3.5-diamino-6-(2-bromo-5-chlorophenyl)-1,2,4-triazine

3,5-diamino-6-(1-naphthyl)-1,2,4-triazine

5-acetamido-3-amino-6-(2,3-dichlorophenyi)-1,2,4-triazine

3-amino-6-(2,3-dichlorophenyl)-5-dimethylaminomethyleneamino-1,2,4-triazine

3,5-diamino-6-(2-methyl-1-naphthyl)-1,2,4-triazine

3,5-diamino-6-(3-chloro-1-naphthyl)-1,2,4-triazine.

The present invention also provides the first practicable medical use of the compounds of the formula (III), as hereinbefore defined. Preferably this will be for the treatment of CNS disorders, and in particular epilepsy, in humans.

In a further aspect, the present invention provides pharmaceutical formulations comprising a compound of the formula (III) in admixture with a pharmaceutically acceptable carrier. Suitable acid addition salts of the compounds of formula (iii) include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. Thus, preferred salts include those formed from hydrochloric, sulphune, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, exalic, fumaric, maleic, exaleacetic, methanesulphonic, p-toluenesulphonic and benzenesulphonio acids.

The compounds of the formula (iii) will be present in the compositions of the present invention in an effective unit dosage form, that is to say in an amount sufficient to be effective against CNS disorders in

The pharmaceutically acceptable carriers present in the compositions of this invention are materials recommended for the purpose of administering the medicament. These may be liquid or solid materials, which are otherwise inert or medically acceptable and are compatible with the active ingredients.

These pharmaceutical compositions may be given orally or parenterally, used as a suppository, or applied topically as an ointment, cream or powder. However, oral and parenteral administration of the compositions are preferred.

For oral administration, fine powders or granules will contain diluting, dispensing and/or surface active agents, and may be presented in a draught, in water or in a syrup, in capsules or sachets in the dry state or in non-aqueous suspension wherein suspending agents may be included, or in a suspension in water or syrup. Where desirable or necessary, flavouring, preserving, suspending, thickening or emulsifying agents can be included.

When a suspension is prepared in water according to the present invention at least one such agents will be present.

For parenteral administration, the compounds may be presented in sterile aqueous injection solutions which may contain anti-oxidants or buffers.

As stated above, the free base or a salt thereof may be administered in its pure form unassociated with other additives in which case a capsule or sachet is the preferred carrier.

Alternatively the active compound may be presented in a pure form as an effective unit dosage, for instance, compressed as a tablet or the like.

Other compounds which may be included are, for example, medically inert ingredients, e.g. solid and liquid diluents such as lactose, starch, or calcium phosphate for tablet or capsules; olive oil or ethyl cleate for soft capsules; and water or vegetable oil for suspensions or emulsions; lubricating agents such as talc or magnesium stearate; gelling agents such as colloidal clays; thickening agents such as gum tregacanth or sodium alginate; and other therapeutically acceptable accessary ingredients such as humectants, preservatives, buffers, and antioxidants which are useful as carriers in such formulations.

Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the formula (III) which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 250 mg.

The pharmaceutical compositions of the present invention will be prepared by the admixture of a compound of the formula (III) with a pharmaceutically acceptable carrier. Conventional pharmaceutical excipients may be admixed as required.

The present invention provides a method of treatment of convulsions in mammals, and particularly epilepsy in humans by the administration of a non-toxic anticonvulsant effective amount of a compound of the formula (III) or a pharmaceutically acceptable salt, or a composition as hereinbefore defined.

As Indicated above, the compounds of the formula (III) are generally useful in treating such as disorders by oral administration or injection (i.p. or s.c.).

The compounds of the formula (III) are normally administered orally at a dose of from 0.1 mg/kg. to 30 mg/kg. per day. The dose range for adult humans is generally from 8 mg. to 2,400 mg/day and preferably 35 to 1,050 mg/day. Due to the fact that the compounds of the formula (III) are extremely long acting, it may often be advantageous to administer an initial dose of 70 to 2,400 mg. the first day then a lower dose of 20 to 1,200 mg. on subsequent days.

The present invention also provides a process for the preparation of compounds of the formula (III) which comprises the cyclisation of a compound of the formula (IV):

$$\begin{array}{c|c}
 & R^9 & R^{10} & NH \\
 & NNH \cdot CNH_2 \\
 & CCN \\
 & R^6
\end{array}$$
(IV)

wherein R<sup>a</sup>—R<sup>10</sup> are as hereinbefore defined; and thereafter, where desired substituting the amino group adjacent to the phenyl ring to give a group R<sup>11</sup> wherein R<sup>11</sup> is as hereinbefore defined other than amino, by conventional methods.

This cyclisation reaction is normally carried out by refluxing in an alkanol, preferably a  $C_{1-1}$  alkanol such as methanol or ethanol, in the presence of a strong base such as potassium hydroxide.

The preparation of the compounds of the formula (IV) is analogous to that described in the literature, i.e. U.S. Patent No. 3,637,688, for structurally related compounds.

The following examples illustrate the preparation of the compounds of the invention and their CNS activity.

#### Example 1

Preparation of 3.5-diamino-6-(2.3-dichlorophenyl)-1,2,4-triazine. 2.3-Dichlorobenzoic Acid

36

A solution of 2,3-dichlorolodobenzene (37.3 g, 0.14M) in sodium dried ether (300 mls) was added dropwise to magnesium turnings (3.65 g, 0.15 gm Atm) and a crystal of lodine with warming so as to form a Grignard reagent.

The mixture was stirred and refluxed for 2 hours then cooled and transferred dropwise, under nitrogen; into a stirred mixture of sodium dried ether (250 mls) containing solid carbon dloxide (ca. 100 g). The mixture was stirred for 2 hours, left overnight to warm to room temperature, then treated with ice (ca. 150 g) and 2N aqueous hydrochloric acid (75 mls), and the product extracted with ether (200, 100 and 50 mls). The combined ether extracts were washed with water (2 × 40 mls) then repeatedly extracted with 2N aqueous sodium hydroxide (100, 50 and 50 mls). These basic solutions were combined, stirred with activated charcoal (3 g) for 10 minutes, filtered and the cooled filtrate was acidified with concentrated hydrochloric acid (25 mls) at 10°C. The resultant solid was filtered off, washed with water (2 × 20 mls) and dried in vacuo. Yield 20.76 g (77.6%), m.p. 167—169°C (uncorrected).

2,3-Dichlorobenzoyi Chloride

A mixture of 2.3-dichlorobenzoic acid (39.4 g 0.2M) and thionyl chloride (100 mls) was heated to reflux for 2½ hours. The cooled solution was evaporated down in vacuo and distilled under nitrogen. Yield 35.5 g (85%), b.p. 146—148°C at 31 mm of mercury pressure.

2,3-Dichlorobenzoyi Cyanida

15

36

A mixture of cuprous cyanide (36.9 g, 0.41M), potassium iodide (68.5 g, 0.41M) and xylene (400 mis) was refluxed in an atmosphere of nitrogen under a Dean and Stark trap for 24 hours so as to remove all trace of water.

A solution of 2,3-dichlorobenzoyl chloride (35.5 g, 0.17M) in sodium dried xylane (130 mls) was added dropwise to the above mixture of dry cuprous cyanide and xylane. The resulting mixture was stirred and heated to reflux for a further 72 hours. The cooled mixture was filtered and the solid washed well with sodium dried xylane (200 mls). The filtrate and washings were combined and evaporated down in vacuo to give an oil. Yield 32 g (94%).

3,5-Diamino-6-(2,3-dichiarophanyi)-1,2,4-titlazine

A solution of 2,3-dichlorobenzoyl cyanide (32 g, 0.16M) in dimethylsulphoxide (80 mls) was added dropwise to a stirred suspension of aminoguanidine bicarbonate (81.67 g, 0.6M) which had been treated with 8N equeous nitric acid (400 mls) at a temperature of ca 25°C. The mixture was stirred for 3 hours, then left to stand at room temperature for 7 days. The cooled mixture was stirred and basified with 0.880 aqueous ammonia (400 mls) at 20°C, then stirred with ice cooling for 30 minutes, filtered and the resulting solid washed thoroughly with water and finally dried in vacuo.

The above solid was added to a 10% solution of poisssium hydroxide pellets in methanol (400 mis) and the solution heated to refluxed for 1½ hours. When cool the solution was evaporated down in vacuo, treated with ice water (800 mis) then stirred for 30 minutes and filtered. The residue was dried and recrystallised from isopropanol to give 3,5-diamino-6-(2,3-dichlorophenyi)-1,2,4-triazine. Yield 6.8 g (15.6%), m.p. 216—218°C (uncorrected).

Example 2

By a method analogous to that described in Example 1 the compounds listed in Tables 1 and 2 were prepared:

TABLE 1

V; R	m.p. (uncorrected)	% Yield (from acid)
2,5Cl <sub>2</sub> .	228-230°C 2	
2-CI, 4-Br	223-225°C	6
2C1, 5Br	238-240°C	2
2-CF,	177-178°C	0.4
2-CI, 6-F	229-228°C	14.5
2Me	181-183°C	<b>25</b> .
· 2—Br .	204–207°C	34
2-1	219-222°C	7
2-Br, 5-Cl	255-256°C	1.2

68

60

60

#### TABLE 2

VI; R	m.p. (uncorrected)	% Yield (from aoid)
н	215216°C	7.5
2-Me	131~134°C	0.3
3CI	285-288°C	1.0

#### Example 3

# 28 Preparation of 3,5-diamino-8-(2,3,5-trichlorophenyi)-1,2,4-triazine

#### 2,3,5-Trichlorobenzoic Acid

20

Powered sodium nitrite (37.0 g, 0.54M) was added portionwise to concentrated sulphuric acid (270 ml) which was stirred under an atmosphere of nitrogen. The temperature of the mixture was not allowed to rise above 70°. Meanwhile 3-amino-2,5-dichlorobenzole acid (100 g, 0.45M) was dissoived in hot glacial acetic acid (1,200 ml), the resultant solution was cooled repidly to room temperature and added dropwise to the above stirred and cooled nitrous acid mixture so that the internal temperature did not rise above 30°. The solution formed after the addition was left at room temperature for 2 hours then was slowly added to a stirred solution of cuprous chlorida (97 g, 0.97M) in concentrated hydrochloric acid (970 ml). The resultant mixture was stirred until the nitrogen evolution had ceased and was then left overnight. The solid was filtered off, washed well with water and dried in vacuo. Yield 90.1 g (89%) m.p. 164—185°C (uncorrected).

## 2,3,5-Trichlorobenzoyi Chioride

A mixture of 2,3,5-trichlorobenzoic sold (90 g, 0.4M) and dimethylformamide (1 ml) in thionyl chloride (200 ml) was heated to reflux for 2 hours. The cooled solution was evaporated down in vacuo and the residue distilled under nitrogen. Yield 89.2 g (90%), b.p. 158—160°C at the pressure of 30 mm of mercury.

# 2,3,5-Trichlorobenzoy! Cyanida

A mixture of cuprous cyanide (89 g. 0.9M), potassium lodide (150.5 g, 0.9M) and xylene (800 ml) was heated to reflux in an atmosphere of nitrogen under a Dean and Stark trep for 24 hours.

A solution of 2,3,5-trichlorobenzoy! chloride (89 g, 0.36M) in sodium dried xylene (100 ml) was added to the above suspension. The resulting mixture was stirred and heated to reflux for a further 72 hours. The cooled mixture was filtered and the solid was washed well with sodium dried xylene (200 ml). The filtrate and washings were combined and evaporated in vacuo to give an oil. Yield 76 g (96%).

## 3,5-Diamino-6-(2,3,5-trichlorophenyl)-1,2,4-triazina

A solution of 2,3,5-trichlorobenzoyl cyanide (38.5 g, 0.16M) in dimethylsulphoxide (80 ml) was added dropwise to a stirred suspension of aminoguanidine bicarbonate (65.76 g, 0.32M) which had been treated with 8N aqueous nitric acid (560 ml). The mixture was stirred for 3 hours and then was left to stand at room temperature for 21 days. The solid was filtered off, washed with water (2 x 100 ml) and dried in vacuo. A suspension of the dried solid in a 10% solution of potassium hydroxide pellets in methanol (320 ml) was heated to reflux for 1 hour, the mixture was cooled and evaporated down in vacuo. The residue was treated with ice/vater (200 ml), the resultant solid was filtered off and dried in vacuo. This dried solid was put on top of a dry column (25 mm diameter, 200 g of MFC silica gel) and eluted with a solution of ethyl acetate/methanol/acetic acid (90:2.5:2.5). Fractions 50 to 80 (900 drops per fraction) were collected, combined and evaporated down in vacuo. The resultant solid was recrystallised from Isopropanol to give 3,5-diamino-8-(2,3,5-trichlorophenyl)-1,2,4-triazine. Yield, 0.77 g (1,6%), m.p. 232—235°C (uncorrected).

Example 4

Preparation of 5-Acetamido-3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine

A solution of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (2 gm, 8mM) and scatic anhydride (10 mis) in acatic acid (20 mis) was stirred and heated to reflux for 2 hours. The solution was then cooled and evaporated down in vacuo. The residue was treated with aqueous 0.880 ammonia (100 mis) and the resultant mixture was stirred for 2 hours. The solid was separated by filtration, dried then recrystallized from isopropenol to give 5-acetamido-3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Yield 1.0 gms (42%), m.p. 250-252° (uncorrected).

Example 5

Preparation of 3-Amino-6-(2,3-dichlorophanyi)-5-dimethyl aminomethyleneamino-1,2,4-triazine oxalate

Dimethylformamide dimethyl acetal (1 ml) was added dropwise to a stirred mixture of 3,5-dlamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (1 g, 4 ml/l) in dry dimethylformamide (20 mls) in a nitrogen atmosphere. The mixture was stirred and heated at 120° for 2 hours, the the resultant solution was cooled and evaporated down in vacuo. The residual oil was washed once with water (20 mls) then dissolved in a solution of oxalic scid (1 gm) in methanol (20 mls). Ether (1 00 mls) precipitated an oil which slowly crystallized. The residue was recrystallized from equeous isopropanol to give 3-amino-6-(2,3-dichlorophenyl)-5-dimethylaminomethyleneamino-1,2,4-triazine oxalate. Yield 0.19 gms (14%), m.p. 172—175°C Dec. (uncorrected).

Example 6

Pharmecological Activity of Compounds of the Present Invention

Tables 3 and 4

The anticonvulsant activity of certain compounds of the present invention was determined by a standard maximal electroshock test, that described by L. A. Woodbury and V. D. Davenport, *Arch. Int. Pharmacodyn.*: 1952, 92, 97.

TABLE 3

50

45

55

VII; R1	vil; R	ED <sub>so</sub> , MES mice, mg/kg, p.o.		
2,3CI,	NH,	2.4		
2,5-Cl <sub>2</sub>	NH <sub>2</sub>	3.3		
2-Ma	NH <sub>2</sub>	15.0		
2C1, 4Br	NH <sub>2</sub>	12.8		
2-CI, 5-Br	NH <sub>2</sub>	0.9		
2-CF,	NH <sub>2</sub>	20.0		
2-Cl, 6-F	NH <sub>2</sub>	12.2		
2,3,5—CI,	NH,	0.65		
2~Br	NH <sub>2</sub>	8.5		
2-1	NH <sub>2</sub>	11.8		
2-Br, 5-Cl	NH <sub>3</sub>	4.6		
2,3-Cl,	инсосн,	5		
2,3-CI,	N=CHNMo,	5		
	1			

TABLE 4

VIII R	ED <sub>so</sub> , MES mice, mg/kg, p.o.
н	2.9
2-Me	16.5
3–CI	· 6.5

The LD<sub>50's</sub> (expressed in mg/kg, p.o.) of 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine and 3,5-diamino-6-(2,5-dichlorophenyl)-1,2,4-triazine were determined in mice and rate. The LD<sub>50</sub> described is the dose for which 50% of the animals survive 10 days after administration of the compound.

. VII R <sup>1</sup>	R	Mice	Rats
2,3-Cl <sub>2</sub>	NH <sub>1</sub>	250	640
2,5-Ci,	· NH;	708	640

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triszine 150 mg
Lactosa 200 mg
Meize Starch 50 mg
Polyvinylpyrrolidone 4 mg
Magnasium Stearate 4 mg

The drug was mixed with the lactose and starch and granulated with a solution of the polyvinylpyrrolidone in water. The resultant granules were dried, mixed with magnesium stearate and compressed to give tablets of average weight 408 mg.

# 50 Claima

60

10

20

30

#### 1. A compound of the formula (III):

$$H_2N - N = N$$
 $H_2N - N = N$ 
 $H_2N$ 

or an acid addition salt thereof, wherein R<sup>o</sup> is chlorina, bromine, iodine, C<sub>1-4</sub> alkyl or trifluoromethyl; R<sup>o</sup> is hydrogen, halogen, C<sub>1-4</sub> alkyl or trifluoromethyl or R<sup>o</sup> and R<sup>o</sup> form a —CH=CH—CH=CH— group optionally substituted by a halogen atom r a C<sub>1-4</sub> alkyl or trifluoromethyl group; R<sup>o</sup> is hydrogen,

bromine, lodine, C<sub>1-4</sub> alkyl or trifluoromethyl; R\* is hydrogen, hetogen, C<sub>1-4</sub> alkyl or trifluoromethyl; R\*\* is hydrogen, methyl or fluorine and R\*\* is amino, C<sub>1-4</sub> acytamino or di-substituted aminomethylene-amino, provided that at most only two of R?—R\*\* are other than hydrogen and that R\*—R\*\* are not all hydrogen when R\* is chlorine.

2. A compound of the formula (III), as claimed in claim 1 herein, wherein R<sup>6</sup> is a chlorine or bromine atom, R<sup>7</sup> is a hydrogen, chlorine or bromine atom or R<sup>6</sup> is linked to R<sup>7</sup> to form a —CH=CH—CH=CH—group, R<sup>8</sup> is a hydrogen, chlorine or bromine atom, R<sup>8</sup> is a hydrogen or bromine atom and R<sup>11</sup> is an amino group.

3. 3.5-Dlamino-6-(2,3-dlchlorophanyl)-1,2,4-triazine.

4. A pharmaceutical composition comprising a compound of the formula (III), as claimed in any of claims 1 to 3 herein, in admixture with a pharmaceutically acceptable carrier.

5. A compound of the formula (III), as claimed in any one of claims 1 to 3 herein, for use in medicine.

 B. A compound of the formula (III) as claimed in any one of claims 1 to 3 for use in medicine in the treatment of epilepsy.

7. A process for the preparation of a compound of the formula (III), as claimed in claim 1 herein, which comprises the cyclisation of a compound of the formula (IV):

wherein R\*—R\* are as defined in claim 1 herein; and thereafter, where desired, substituting the amino group adjacent to the phenyl ring to give a group R\*\* wherein R\*\* is as defined in claim 1 herein other than amino, by conventional methods.

# Patentansprüche

20

28

35

40

**.** 

1. Verbindung der Formel (III)

$$H_2N \longrightarrow N=N$$

$$H_6 \longrightarrow H_8$$

$$H_8$$

$$H_8$$

$$H_8$$

oder ein Säureadditionssalz davon, worin R<sup>o</sup> Chlor, Brom, Jod, C<sub>1,4</sub>-Alkył oder Trifluormethyl; R<sup>7</sup> Wasserstoff, Halogen, C<sub>1,4</sub>-Alkył oder Trifluormethyl oder R<sup>o</sup> und R<sup>7</sup> gemeinsam eine —CH—CH—CH—CH—Gruppe, die gegebenenfalls durch ein Halogenatom oder eine C<sub>1,4</sub>-Alkył oder Trifluormethylgruppe substituiert ist, R<sup>o</sup> Wasserstoff, Brom, Jod, C<sub>1,4</sub>-Alkył oder Trifluormethyl, R<sup>o</sup> Wasserstoff, Halogen, C<sub>1,4</sub>-Alkył oder Trifluormethyl, R<sup>o</sup> Wasserstoff, Methyl oder Fluor und R<sup>o</sup> Aminonethylenamino, mit der Maßgabe bedeuten, daß höchsens zwei der Gruppen R<sup>o</sup> bis R<sup>oo</sup> von Wasserstoff verschieden sind und daß nicht sämtliche Gruppen R<sup>o</sup> bis R<sup>oo</sup> Wasserstoff bedeuten, wann R<sup>o</sup> Chlor derstellt.

R<sup>7</sup> bis R<sup>10</sup> Wasserstoff bedeuten, wenn R<sup>0</sup> Chlor derstellt.

2. Verbindung der Formel (III) gemäß Anspruch 1, dadurch gekennzeichnet, daß R<sup>0</sup> ein Chlor- oder Bromaton derstellt, R<sup>7</sup> ein Wasserstoff-, Chlor- oder Bromaton bedeutet oder R<sup>0</sup> mit R<sup>7</sup> unter Bildung einer —CH=CH—CH=CH—Gruppe verbunden sind, R<sup>0</sup> ein Wasserstoff-, Chlor- oder Bromaton darstellt, R<sup>0</sup> ein Wasserstoff- oder Bromaton bedeutet und R<sup>11</sup> eine Aminogruppe derstellt.

3. 3,6-Diamino-6-(2,3-dichlorphenyl)-1,2,4-triazin.

4. Pharmazeutische Zubereitung entheltend eine Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zusammen mit einem pharmazeutisch annehmbaren Träger.

5. Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medizin.

6. Verbindung der Formel (III) gemäß einem der Ansprüche 1 bis 3 zur Verwendung in der Medizin bei der Behandlung der Epilepsie.

7. Verfahren zur Herstellung einer Verbindung der Formei (III) gemäß Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formei (IV)